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EXAMINER	
NGUYEN, Q	
ART UNIT	**PAPER NUMBER**
1632	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Applicant(s)	
REID ET AL.	
Art Unit	
1632	

-- The MAILING DATE of this communication app... -- correspondence address --

P ri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SE... FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In n... after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statuto... be timely filed be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire S... ys will communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to becom... he mailing date of this ...5 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on ____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the ... is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *36,37,40 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) ____ is/are allowed.

6)☒ Claim(s) *1-35,38,39 and 42-44* is/are rejected.

7)☐ Claim(s) ____ is/are objected to.

8)☐ Claims ____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on ____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on ____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) ____.

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6*.
18) ☐ Interview Summary (PTO-413) Paper No(s). ____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-35, 38, 39 and 42-44, drawn to human liver progenitors, their progeny or more mature forms thereof, a composition comprising an enriched population of the same, methods of providing the same composition, and methods of treating liver dysfunction or disease using the same composition, classified in class 424, subclasses 93.7, 93.21; class 435, subclass 325, for examples.

II. Claims 36-37, drawn to a bioreactor comprising a composition comprising an enriched population of human liver progenitors, their progeny, or more mature forms thereof, which human liver exhibit one or more markers indicative of expression of alpha-fetoprotein, albumin, or both, classified in class 435, subclass 289.1.

III. Claims 40-41, drawn to a cryopreservative mixture for preservation of adherent cells and a method for cryopreservation of adherent cells, classified in class 435, subclass 1.3.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product, or (2) the product as claimed can be used in a materially different process of

using that product (M.P.E.P. 806.05 (h)). In the instant case, the bioreactor of Invention II can be practiced with another materially different product, such as chondrocytes, myocytes or others.

Although there are no provisions under the section for "Relationship of Inventions" in M.P.E.P. § 806.05 for inventive groups that are directed to different methods, restriction is deemed to be proper because these methods appear to constitute patentably distinct inventions for the following reasons: Groups I and III are directed to methods that are distinct both physically and functionally, and are not required one for the other. Invention I requires the use of human liver progenitors, their progeny or more mature forms thereof, in methods of treating liver dysfunction and disease which require different processing steps, desired endpoints and technical considerations from a method for cryopreservation of adherent cells in Invention III.

Inventions II and III are mutually exclusive and independent. The bioreactor of Invention II is not required for a method of adherent cell cryopreservation of Invention III, and vice versa.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone discussion with Attorney Corinne M. Pouliquen on October 26, 2000, a provisional election was made without traverse to prosecute the invention of Group I (Claims 1-35, 38, 39, and 42-44). Affirmation of this election should be made by applicant in replying to this Office action.

Groups II and III are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being for nonelected inventions.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.**

Claims 42-44 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 42-44 are directed to "human liver progenitors". Since the claimed human liver progenitors are not recited as "isolated" or "cultured", the claimed human liver progenitors can not be distinguished from naturally occurring human liver progenitor cells, which is a non-statutory subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 27-35 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 27-34 are directed to a method of treating liver dysfunction or disease responsive to treatment with liver progenitors in a subject in need thereof, comprising administering to the subject an effective amount of human liver progenitors, their progeny, more mature forms thereof, or combinations thereof, in a pharmaceutically acceptable carrier and treating the liver dysfunction or disease.

Claim 35 is directed to a method of treating a disease in a subject in need thereof comprising administering an effective amount of human hepatic progenitors, their progeny, or more mature forms thereof in which the human hepatic progenitors, their progeny, or more mature forms harbor exogenous nucleic acid.

Claim 39 is drawn to a pharmaceutical composition comprising an enriched population of human liver progenitors, their progeny, or more mature forms thereof, which human liver progenitors exhibit one or more markers indicative of expression of alpha-fetoprotein, albumin, or both; and a pharmaceutically acceptable carrier.

The specification teaches the isolation of human liver progenitor cells from fetal and adult human livers. With regard to the nature of the instant claims example 10 of the specification discloses that upon injection of hepatic progenitors infected with

recombinant adenovirus expressing human urokinase plasminogen activator (uPA), into the portal vein of C57BL/6 female mice, hepatic damage and high rates of 3H-thymidine uptake were observed. Transient elevation of serum urokinase reached a peak value at day 4, then fell back to a background level on day 12, while hepatic 3H-thymidine uptake began on day 3 and persisted for 8 days. Although initial moderate inflammatory infiltrate comprising macrophages and neutrophils was noted, by three to four weeks the infiltrate was resolved and the liver appears normal. It was suggested that the urokinase expression in combination with hepatic progenitors induced significant liver parenchymal cell regeneration. The above evidence is noted and considered. However, it can not be extrapolated to the instant claimed invention.

The specification is not enabled for the instant claims because it fails to provide sufficient teachings and guidance demonstrating that by administering human liver progenitors of the present application into a subject having liver dysfunction or disease, the subject would be treated for symptoms associated with the liver dysfunction or disease. There is no apparent correlation between an increase in the uptake of hepatic 3H-thymidine in mice treated with hepatic progenitors infected with recombinant adenovirus expressing human urokinase plasminogen activator (uPA) in example 10 to obtaining any therapeutic effects for treatment method claims. Thus, there is a lack of a nexus between a specific given example provided by the specification and the instant methods of treatment. Nor does the prior art teach such a correlation. In addition, the specification fails to provide specific relevant information such as the effective cell dosages, the frequency of administration and the exact site of introduction for a given

specific liver dysfunction or disease to obtain any therapeutic effects for the claimed treatment methods. Moreover, there is no evidence indicating that the newly introduced human liver progenitors are properly engrafted, proliferated, and differentiated into mature and functional liver cells in any treated subject. The mere mentioning of advantages offered by human liver progenitors for *ex vivo* gene therapy and routes of tranplantation (See specification, pages 40-44) is not seen as providing enablement as there is no correlation between these and a therapeutic outcome. Without the specific teaching or guidance provided by the specification, it would have required undue experimentation for one skilled in the art to use the instant claimed invention. The CAFC has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genetech, Inc. v. Novo Nordisk A/S*, 42 USPQ 2d 1001, at 1005).

With regard to the breadth of claim 35 encompassing human hepatic progenitors, their progeny, or more mature forms thereof comprising any and all exogenous nucleic acid to treat a disease in a subject, the specification fails to teach any specific vector used to deliver and express a specific gene (a therapeutic protein) in human hepatic progenitor cell populations of the instant claimed invention for treating a specific disease. At the effective filing date of the present application, it has been noted that sub-optimal vectors and the lack of long-term and stable transgene expression are

some of the factors limiting an effective gene therapy. In a review on gene delivery systems available for gene therapy (Methods of gene delivery, Hematol. Oncol. Clin. North Am. 12:483-501, 1998), Wivel and Wilson stated that "One of the major challenges still confronting the field is the design of more efficient vectors. The gene delivery systems being used today will undoubtedly be seen as crude when compared with future developments. It is unlikely that there will ever be a universal vector, but rather there will be multiple vectors specifically designed for certain organ sites and certain diseases...It will be necessary to do much more fundamental research in cell biology, virology, immunology, and pathophysiology before vectors can be significantly improved." (pages 498-499 in Summary section). Additionally, factors such as the level of mRNA produced, the stability of the protein produced, the protein's compartmentalization within the cell or its secretory fate differ dramatically based on which protein being produced, and therefore the desirable therapeutic effect sought to achieve. Thus, the level of gene expression, its duration, and its *in vivo* therapeutic effects are not always predictable, and they can not be overcome with routine experimentation.

Accordingly, due to the lack of direction, guidance presented in the specification regarding to the administration of human liver progenitors, their progeny , more mature forms thereof to treat liver dysfunction or disease in a subject, the absence of working examples, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make/use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 1-11, 12-20, 21-26, 38, 39 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "substantially", "relatively large size" and "relatively small size" in claim 1 are relative terms which render the claim indefinite. The terms "substantially", "relatively large size" and "relatively small size" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Clarification is requested.

In claims 1, 10, 21 and 42, the phrase "one or more markers indicative of expression of alpha-fetoprotein, albumin, or both" is vague and unclear, and therefore the metes and bound of the claim can not be exactly determined. What are the markers? Clarification is requested.

In claim 3, the term "less than about 15 microns" is vague and therefore renders the claim indefinite. Would 15 microns meet the recited limitation?

Claim 12 is incomplete because the claim lacks a step (or steps) which links step (a) that of providing a substantially single cell suspension of human liver tissue, and step (b) that of subjecting the suspension to a positive or negative immunoselection, to the preamble of "providing a composition comprising an enriched population of human

liver progenitors". In addition, the term "substantially single cell suspension" is a relative term which renders the claim indefinite.

In claim 17, the phrase "an adult liver cell-specific marker" is vague and thus it renders the claim indefinite. The metes and bound of the claim can not be clearly determined.

In claim 21, the phrase "which human liver exhibit one or more markers" is unclear and renders the claim indefinite. Should human liver progenitors, their progeny or more mature forms thereof exhibit the markers? Clarification is requested.

Claim 35 is incomplete because the claim lacks a step (or steps) which links the step of administering an effective amount of human hepatic progenitors, their progeny or more mature forms thereof, to the preamble "treating a disease in a subject".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-8, 10-16, and 18-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Muench et al. (Blood 83:3170-3181, 1994) or Muench et al. (Blood 89:1364-1375, 1997).

Claims 1- 8 and 10 are drawn to a method of providing a composition comprising a mixture of cells derived from human liver tissue, which mixture comprises an enriched population of human liver progenitors, the method comprising (a) providing a single cell suspension of human liver tissue, (b) debulking the suspension under conditions that permit the removal of mature cells, while retaining immature cells, to provide a mixture of cells comprised an enriched population of human liver progenitors which human liver progenitors themselves, their progeny, or more mature forms thereof express alpha-fetoprotein, albumin, or both. Claim 11 is directed to a human liver progenitor isolated by the same method.

Claims 12-16, 18 and 19 are drawn to a method of providing a composition comprising an enriched population of human liver progenitors comprising (a) providing a substantially single cell suspension of human liver tissue, and (b) subjecting the suspension to a positive or negative immunoselection. Claim 20 is directed to a human liver progenitor isolated by the same method.

Muench et al. (1994, 1997) disclosed a method for the isolation of human fetal liver progenitors and hematopoitic stem cells derived from human fetal liver. The method comprises subjecting a suspension of fetal liver cells to a density centrifugation to obtain light density fetal liver (LDFL) cells (See column 1, page 3171, Muench et al., 1994; column 2, first paragraph, page 1365, Muench et al., 1997). LDFL cells were

depleted of glycophorin A (GPA^-) cells by immunomagnetic beads depletion, then GPA^- LDFL cells were enriched for $CD34^+$ cells by panning using an anti-CD34 antibody-coated tissue culture flasks. GPA^- LDFL cells were also fractionated based on cell-surface antigen expression by FACS (See column 1, page 3171, Muench et al., 1994; column 2, first paragraph, page 1365, Muench et al., 1997). As the method of Muench et al. (1994, 1997) and the method claimed can not be distinguished, the method of Muench et al. inherently produces an enriched population of human liver progenitor cells as claimed. Therefore, the references clearly anticipate the claimed invention.

Claims 21-23 and 42-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Muench et al. (Blood 83:3170-3181, 1994) or Muench et al. (Blood 89:1364-1375, 1997).

Claims 21-23 are drawn to a composition comprising an enriched population of human liver progenitors, their progeny, or more mature forms thereof, which human liver progenitors exhibit one or more markers indicative of expression of alpha-fetoprotein, albumin, or both; the same composition wherein the progenitors comprise hepatic progenitors, hemopoietic progenitors, mesenchymal progenitors, or combinations thereof, and the same wherein said human liver progenitors, their progeny, or more mature forms thereof express CD14, CD34, CD38, CD117, ICAM or combinations thereof. Claim 42 is directed to isolated human liver progenitors, their progeny or more mature forms whereof which exhibit one or more markers indicative of expression of alpha-fetoprotein, albumin, or both. Claims 43-44 are drawn to isolated human liver

progenitors, their progeny or more mature forms thereof which exhibit the phenotype glycophorin A^-, $CD45^-$, alpha-fetoprotein^{+++}, albumin$^+$, and $ICAM^+$, and the same which further express $CD14^+$, $CD34^{++}$, $CD38^{++}$, $CD117^{+++}$, or combinations thereof.

Muench et al. (1994) disclosed the isolation of human fetal liver progenitors with a high proliferative potential and a phenotype of $CD34^+$, $CD33^+$, $CD13^+$, CD38-, lin^- (lineage= CD3, CD8, CD10, CD14, CD15, CD16, CD19, CD20 and glycophorin A), $CD45RA^-$, $CD45RO^-$, $CD71^-$, and heterogeneous *for c-kit* or CD117 (See abstract and page 3171). Muench et al. (1997) disclosed the isolation of hematopoietic stem cells derived from human fetal liver, with a phenotype of $CD4^+$, $CD34^{++}$, Lin^-, $CD117^+$, $CD38^-$, $CD45RA^-$ (See abstract and page 1365). As the method of Muench et al. (1994, 1997) and the method claimed can not be distinguished, the method of Muench et al. inherently produces an enriched population of human liver progenitor cells as claimed. Therefore, the references clearly anticipate the claimed invention.

Claims 1-16, 18-23, and 42-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Craig et al. (J. Exp. Med. 17:1331-1342, 1993).

Craig et al. disclosed the isolation of human hematopoietic progenitor cells derived from human fetal liver with a phenotype of Thy-1^+, $CD34^+$, $CD38^{low}$, $CD45RA^-$, $CD45RO^+$, $CD71^{low}$, and $CD117^{low}$ (See abstract, and column 1, second paragraph, page 1332). The method comprises the preparation of low density mononuclear cells by density centrifugation using Ficoll-Paque (column 1, page 1332, lines 24-26). In some samples, red blood cells were lysed by the addition of 10-fold excess of

ammonium chloride lysing solution (column 1, page 1332, lines 30-32). Subpopulations of low density mononuclear cells were subsequently sorted by multiparameter flow cytometry (column 2, page 1335, second paragraph). As the method of Craig et al. (1993) and the method claimed can not be distinguished, the method of Craig et al. inherently produces an enriched population of human liver progenitor cells as claimed. Thus, the reference clearly anticipates the claimed invention.

Claims 11, 20, 21-26 and 42-44 rejected under 35 U.S.C. 102(e) as being anticipated by Faris (U.S. Patent No. 6,129,911 with an effective filing date of 7/10/1998).

Claims 21-26 are drawn to a composition comprising an enriched population of human liver progenitors, their progeny, or more mature forms thereof, which human liver progenitors exhibit one or more markers indicative of expression of alpha-fetoprotein, albumin, or both; the same composition in which progenitors habor exogenous nucleic acid promoting the expression of at least one polypeptide of interest. Claims 11 and 20 are directed to a human liver progenitor isolated by the methods of claims 1 and 14, respectively. Claims 41-43 are drawn to isolated human liver progenitors encompassing hepatic progenitors.

Faris taught the preparation and isolation of a liver cell cluster of less than 10 cells comprising a liver stem cell and a hepatocyte, and a primary liver stem cell derived from human liver tissue, in which said stem cell comprises DNA encoding a heterologous polypeptide, such as ornithine transcarbamylase, glutamine synthetase,

Factor XIII, Factor IX and others (See columns 1-3, and the claims). The primary liver stem cell derived from human liver tissue is defined as undifferentiated cell that differentiates into a mature functional hepatocyte or bile duct cell (column 1, lines 37-39) which is consistent with the definition of hepatic progenitors of the instant claimed invention (cells give rise to hepatocytes and biliary cells, page 22, lines 3-4). As the method of Faris and the method claimed can not be distinguished, the method of Faris inherently produces an enriched population of human liver progenitor cells as claimed Therefore, the reference clearly anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8, 10, 12-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reid et al. (U.S. Patent No. 6,069,005).

Reid et al. disclosed a method of isolating hepatic progenitors from rat fetal livers utilizing panning techniques and flow cytometry on single cell suspension of liver cells (See claim 1, column 20). The method comprises the panning and fluorescence activated cell sorting of fetal liver cells using specific antibodies to remove mature hepatocytes, mature bile duct cells, endothelial cells, mesenchymal cells and hemopoietic cells for obtaining a cell population enriched for immature hepatic cell types which were subsequently separated into distinct subcategories by multiparametric fluorescence activated cell sorting (See Examples I and II). Since a product and its properties can not be separated, hepatic progenitors isolated by the disclosed method also possess markers indicative of expression of alpha-fetoprotein, albumin, or both (full-length mRNAs, for examples), as well as alpha-fetoprotein-like immunoreactivity, albumin-like immunoreactivity, or a combination thereof. It is further noted that fetal liver cells selected for flow cytometry in the disclosed method have a broad range in cell size, 5 to 15 microns (See column 17, lines 50-51). Although Reid et al. did not specifically teach a method of providing a composition comprising a mixture of cells derived from human liver tissue or an enriched population of human liver progenitors, Reid et al. stated that their method offers a systematic approach to isolating hepatoblasts (hepatic progenitors) from any age from any species (column 2, lines 45-49).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify the method disclosed by Reid et al. by replacing rat fetal liver tissue as the starting material with human liver tissues. The motivation for one carry out the above modification is to obtain a composition enriched in a population of human liver progenitors for cellular characterization as well as for cell transplantation studies. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 21, 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muench et al. (Blood 83:3170-3181, 1994) or Muench et al. (Blood 89:1364-1375, 1997) in view of Reid et al. (U.S. Patent No. 5,789,246, PTO-1449 AB).

The claims are drawn to a composition comprising an enriched population of human liver progenitors, their progeny, or more mature forms thereof, which human liver progenitors exhibit one or more markers indicative of expression of alpha-fetoprotein, albumin, or both; and a cell culture comprising the same composition, an extracellular matrix component, and a culture medium (Claim 38).

Muench et al. (1994) disclosed the isolation of human fetal liver progenitors with a high proliferative potential and a phenotype of $CD34^+$, $CD33^+$, $CD13^+$, CD38-, lin^- (lineage= CD3, CD8, CD10, CD14, CD15, CD16, CD19, CD20 and glycophorin A), $CD45RA^-$, $CD45RO^-$, $CD71^-$, and heterogeneous *for c-kit* or CD117 (See abstract and page 3171). Muench et al. (1997) disclosed the isolation of hematopoietic stem cells derived from human fetal liver, with a phenotype of $CD4^+$, $CD34^{++}$, Lin^-, $CD117^+$, $CD38^-$,

$CD45RA^-$ (See abstract and page 1365). As the method of Muench et al. (1994, 1997) and the method claimed can not be distinguished, the method of Muench et al. inherently produces an enriched population of human liver progenitor cells as claimed. However, Muench et al. (1994, 1997) did not teach a cell culture comprising these cell populations, an extracellular matrix component, and a culture medium. However, Reid et al. taught a cell culture comprising hepatocyte precursors being plated on or in a matrix of collagen type IV and in the serum-free, hormonally defined medium (See columns 2-4) for the expansion or proliferation of hepatocyte precursors.

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to adopt the cell culture system taught by Reid et al. for the expansion of human fetal liver progenitors and hematopoietic stem cells derived from human fetal liver disclosed by Muench et al. (1994, 1997). One would have been motivated to carry out the above modification for expanding human fetal liver progenitors and hematopoitic stem cells for uses in artificial livers, for toxicology and pharmacology studies (See abstract in Reid et al.). Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Deborah Crouch, Ph.D., may be reached at (703) 308-1126, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Quang Nguyen, Ph.D.
Examiner, AU 1632